

Acetylcodeine as a Urinary Marker to Differentiate the Use of Street Heroin and Pharmaceutical Heroin

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Abstract

Acetylcodeine (ACOD) is a synthesis byproduct present in street heroin but not in pharmaceutical diacetylmorphine (DAM) as used in the Swiss program Heroin-Assisted Treatment for Opiate Dependent Drug Users (HAT). ACOD was evaluated and validated as an urine marker to detect the consumption of street heroin by HAT participants. A gas chromatography-mass spectrometry method allowing the quantitation of ACOD concentrations as low as 0.2 ng/mL urine has been developed. In opiate-naïve subjects, intravenous (i.v.) ACOD showed a plasma elimination half-life of 237 ± 18 min, urine peak concentrations 2 h after administration, and a detection window of 8 h. Only $0.4 \pm 0.1\%$ was excreted unchanged, with codeine (COD) as the main metabolite. ACOD may be formed by transacetylation when i.v. DAM and oral codeine are co-administered. To avoid false-positive results, the calculation of COD/ACOD ratios is recommended. In a study with 105 HAT participants, 14% of the tested urines were ACOD positive. Only a low correlation was found between the anonymously self-declared consumption of street heroin and the ACOD positive rate.

Introduction

Between 1994 and 1996 the Swiss Federal Office of Public Health (SFOPH) conducted a research and feasibility study consisting of the dispensation of diacetylmorphine (DAM, heroin), morphine, and methadone to 1035 heavy opiate dependents in 15 Swiss cities (1,2). Since 1999, this project has been running under the name Heroin-Assisted Treatment for Dependent Drug Users (HAT). Under strictly medicinally controlled conditions, single intravenous (i.v.) and oral doses of 50–200 mg (up to 1000 mg/day) of pharmaceutically pure DAM are administered to about 900 therapy-resistant heroin dependents. It is one of the primary goals of HAT to continuously reduce the DAM dose, ideally to zero. However, some heroin

dependents complain about insufficient doses and claim that street heroin is, for whatever reason, more pharmacologically efficient. This motivates them to visit the street heroin market, which increases the not tolerated consumption of illegal street heroin. Therefore, the frequency of visits of the street heroin market and the consumption of illegal street heroin are among several quality parameters for checking the efficiency of the HAT programs.

The analysis of 170 heroin specimens collected between 1991 and 1996 in the street heroin market of Bern revealed the presence of acetylcodeine (ACOD) in more than 95% of the samples (3,4). The concentration of this impurity of manufacture, formed during the acetylation process, varied between 1 and about 5%. In heroin samples confiscated in Switzerland between 1991 and 1999, ACOD was detected in all of the 3489 analyzed samples (5). The ACOD concentration in illicit heroin may reach up to 45% relative to DAM (6). Two studies performed in the United States (7) and in Switzerland (8) showed the presence of ACOD in 37 and 86% of urines from street heroin users, respectively. On the other hand, ACOD was not detected in the pharmaceutical DAM used in HAT or in urine specimens from HAT participants who had received pharmaceutical DAM under strictly controlled clinical conditions and had not consumed street heroin during treatment (8,9). ACOD was therefore evaluated as a potential urine marker to reveal recent concurrent use of pharmaceutical DAM and street heroin. In the first study ("pilot study"), 34% of urine specimens collected unannounced and on the same day from randomly selected HAT participants ($n = 80$) tested positive for ACOD (10). ACOD as a biomarker for long-term consumption of street heroin was also tested in hair obtained from HAT participants and from subjects who had died from fatal opiate overdoses (11). Whereas ACOD was detected in 44% of the samples from the intoxication cases, none of the HAT specimens contained this marker. However, Staub et al. (12) recently found ACOD in 12% of hair samples from another population of HAT participants.

It was the aim of the present study to investigate the pharmacokinetics of i.v. administered ACOD in healthy volunteers, the possible formation of ACOD artifacts, and the feasibility

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and reliability of an ACOD urine monitoring to differentiate the use of street heroin and "state" heroin. For that purpose, urine specimens collected randomly and unannounced from HAT participants in several Swiss cities were analyzed by gas chromatography-mass spectrometry (GC-MS).

Experimental

Materials

ACOD hydrochloride (purity: 96.5%) and ACOD- d_3 hydrochloride (purity: 94.8%) were synthesized in our laboratory (now also available through Lipomed, Arlesheim, Switzerland). Codeine (COD)- d_3 was supplied by Lipomed. COD phosphate was purchased from Merck, and COD phosphate tablets (50 mg) were obtained from Knoll (Liestal, Switzerland). Isolute HXC 300 mg/3 mL solid-phase extraction (SPE) cartridges (International Sorbent Technology, Mid-Glamorgan, U.K.) were provided by ict AG (Basel, Switzerland). The Front-line® immunoassay (Boehringer Mannheim, Mannheim, Germany) used to screen for cocaine was purchased from Roche Diagnostics Corp. Switzerland. All chemicals were of analytical grade.

Methods

Subjects and clinical studies. Ten healthy, opiate-naïve volunteers (5 male, 5 female; mean age 29.1 years) participated in the pharmacokinetic study, conducted at the Clinical Investigation Unit (CIU) of the University Hospital of Bern. The subjects were informed about the risks of the study and gave their written informed consent. The study has been approved by the Ethics Committee of the Faculty of Medicine, University of Bern. Each subject received 5 mg ACOD as a single i.v. bolus dose. Total urine specimens were collected 10 min before and 2, 4, 8, 12, 24, and 48 h after administration and stored at -20°C until analysis. Blood (5–10 mL) was

collected through a peripheral vein catheter 5 min before and 5, 10, 20, 40, 60, 120, 240, 480, and 720 min after dosing. The heparinized blood samples were centrifuged for 10 min at 2000 rpm, and the plasma was instantly deep-frozen and stored at -20°C .

To check for a possible formation (transacetylation) of ACOD when co-administering COD and DAM, a 50-mg COD tablet was given to 10 HAT participants (informed consent, protocol approved by the local Ethics Committee) 30 min prior to an i.v. dose of 120–400 mg DAM (individually given by the HAT protocol). Urine specimens were collected 10 min before and 2, 4, and 8 h after DAM administration.

For the feasibility study ("field study"), urine specimens from 105 HAT participants in the cities of Bern, Thun, and Basel were collected randomly and unannounced on several days in July and August 2000, between 7 and 9 a.m. or 4 and 7 p.m.

Sample extraction. The extraction of ACOD, ACOD- d_3 , and COD from urine was performed by adding 10 mL of 0.03M phosphate buffer (pH 7.0) and 5 μL of the internal standard solution (corresponding to 50 ng ACOD- d_3) to a 10-mL aliquot of the centrifuged urine sample. After brief shaking, the sample was transferred onto the SPE column, preconditioned with 3 mL of methanol and 3 mL of water, and drawn slowly through the column (1–2 mL/min, slight vacuum, without drying out). Six milliliters of water, 6 mL of 0.1M acetate buffer and 6 mL of methanol were used for washing (1–2 mL/min, slight vacuum, without drying out). After eluting with 4 mL dichloromethane/2-propanol/ammonia (80:20:2, v/v) and drying under vacuum, the eluate was evaporated under nitrogen, the residue reconstituted in 80 μL of isooctane by sonication for 5 min, and 3 μL used for GC-MS analysis.

The extraction of ACOD, ACOD- d_3 , and COD from plasma was performed by adding 1 mL of 0.03M phosphate buffer (pH 7.0) and 5 μL of the internal standard solution to a 1-mL aliquot of the centrifuged plasma sample. The SPE procedure was the same as used for urine extraction.

GC-MS analysis. The quantitation of ACOD, ACOD- d_3 , and COD in urine and plasma was performed on a GC-MS system consisting of an HP 5890A series II GC with electronic pressure control, an HP 7673A autosampler, an HP 5972 mass selective detector (MSD) operated in the selected ion monitoring (SIM) mode, and HP 5895A Chemstation software. Chromatographic separation was achieved on a J&W Scientific DB-5 MS capillary column (25 m \times 0.2-mm i.d., 0.33- μm film thickness) and helium at 20.4 cm/s as carrier gas. The oven temperature was initially held 1 min at 180°C , then increased to 280°C at a rate of $10^{\circ}\text{C}/\text{min}$, and held at 280°C for 14 min. The injector and transfer line temperatures were 260 and 280°C , respectively. The injector was operated in the splitless mode.

Peak assignment of ACOD was achieved by comparison of the retention time and the relative abundance of the three characteristic ions m/z 341, 282, 229 with the deuterated in-

Table I. Plasma Levels of ACOD in Opiate-Naïve Subjects ($n = 10$) after an i.v. Bolus of 5 mg ACOD

Subject	Time (min)									
	0	5	10	20	40	60	120	240	480	720
ACOD concentration (ng/mL)										
A	0	2681	640.8	210.3	92.7	51.3	45.3	15.8	8.4	8.0
B	0	4226	684.8	324.9	170.3	64.6	32.3	26.4	21.9	3.8
C	0	2014	104.9	20.2	8.0	3.6	0.5	0.7	0.5	0.7
D	0	1222	285.9	112.1	63.1	50.8	15.1	9.0	5.8	4.9
E	0	3540	295.0	68.5	111.9	38.0	15.5	9.0	5.8	4.7
F	0	966.2	176.0	89.9	55.1	40.4	18.5	8.7	5.7	2.5
G	0	1264	240.5	328.8	74.6	25.5	16.7	7.9	6.6	4.3
H	0	2593	247.0	216.6	71.5	43.2	25.3	17.1	6.1	0.5
I	0	800.4	403.8	109.7	104.9	47.2	20.1	5.6	5.5	4.2
K	0	1311	217.5	119.1	54.5	20.0	22.9	12.1	5.7	5.5
Mean	0	2062	329.6	160.0	80.7	38.5	21.2	11.2	7.2	3.9
SEM	0	368.7	60.8	33.5	13.7	5.6	3.7	2.3	1.8	0.7

ternal standard ACOD-d₃ (m/z 344, 285, 232). COD was identified by the ions m/z 162, 229, 299. Quantitation of ACOD and COD was based on the peak area of the ion m/z 341 and 299, respectively, versus the peak area of the ACOD-d₃ ion m/z 344. Calibration was performed in the range of 0.25 to 25 ("low") and 25 to 250 ng ("high") ACOD and COD per milliliter urine and plasma.

Pharmacokinetic data analysis. Based on the noncompartmental model, all pharmacokinetic parameters were assessed by use of standard calculation procedures performed by the Topfit (version 2.0) computer software (13). The linear trapezoidal rule was implemented for calculations of areas under the plasma concentration-time curves (AUC). The AUCs were extrapolated to infinity ($AUC_{0 \rightarrow \infty}$) by adding the last quantitated concentration (at 720 min) divided by the elimination constant (λ_z).

Results and Discussion

Method

The SPE procedure showed ACOD and COD recoveries from urine and plasma in the range of 84 to 92%, determined at the 1- and 25-ng/mL concentration levels (CV 4–6%, $n = 4$). Two calibration graphs were established to cover the broad range of analyte concentrations. The "low" calibration graph (0.25–25 ng/mL ACOD and COD) was used when the peak-area ratio of ACOD and COD versus ACOD-d₃ was ≤ 5.50 and ≤ 7.39 , respectively. The "high" calibration graph (25–100 ng/mL ACOD, 25–250 ng/mL COD) was used, when the ratio was ≥ 5.51 and

≥ 7.40 , respectively. Correlation coefficients (r) between 0.995 and 0.999 indicate good linearity between analyte concentrations and corresponding MS detector response for both calibration ranges. The interday precision (CV, $n = 5$) of the ACOD and COD quantitation was between 6 and 15% at the 25 and 0.25-ng/mL concentration level, respectively. With a signal-to-noise ratio of 6:1, the limit of quantitation (LOQ) in urine and plasma was 0.20 ng/mL ACOD and COD, whereas the limit of detection (LOD) was 0.10 ng/mL. The internal standard ACOD-d₃ contained about 1% of undeuterated ACOD. In order to avoid false-positive results, this fact was taken in account when determining the LOQ of ACOD. No significant loss of ACOD by in vitro desacetylation to COD could be observed in blood and urine specimens within at least 6 months when instantly deep-frozen after sampling and stored at -20°C .

Pharmacokinetics of ACOD

After i.v. administration (bolus) of 5 mg ACOD to opiate-naïve subjects ACOD plasma peaks (C_{\max}) of 800 to 4226 ng/mL (mean \pm SEM: 2062 ± 369 ng/mL) occurred after 5 min (Table I and Figure 1). The plasma elimination half-life ($t_{1/2}$) was 110 to 311 min (237 ± 18 min), the volume of distribution (V_z) 27 to 185 L (81 ± 15 L), and the total clearance (CL_{tot}) 97 to 314 mL/min (228 ± 29 mL/min). The pharmacokinetics of i.v. ACOD are summarized in Table II. All subjects excreted the highest ACOD concentrations in the 2-h urine (Table III). Peak ACOD concentrations varied between 4.9 and 471.9 ng/mL (mean 98.7 ± 44.2 ng/mL). In the 4-h urine, the ACOD ranged from 0.1 to 11.6 ng/mL (2.9 ± 1.3 ng/mL). The total amount of ACOD excreted with urine within 48 h was 2.7 to 61.5 μg (19.3 ± 5.7 μg), corresponding to only 0.1 to 1.2% ($0.4 \pm 0.1\%$) of the dose administered. Eight hours after administration the ACOD levels were below the LOQ. COD was the main urinary metabolite of ACOD (COD conjugates were not determined). With 566.9 to 8351.3 ng/mL, the highest concentrations of COD were also measured in the 2-h urines (1716.6 ± 798.5 ng/mL) demonstrating the rapid desacetylation of ACOD. The COD/ACOD ratios varied from 1 to 1704 (191 ± 168 , 2-h urine) and 45 to 3614 (480 ± 343 , 4-h urine), respectively.

Formation of ACOD by transacetylation of COD

A controlled clinical study with HAT participants revealed, that ACOD is formed when high i.v. doses of DAM (120–400 mg) and oral COD (50 mg, e.g., as cough medication) are administered simultaneously (Table IV). ACOD concentrations ranged from 0 to 147.0 ng/mL, with mean peak concentrations of 33.6 ± 15 ng/mL in the 2-h urine samples. ACOD was also formed in the GC-MS after injection of an urine extract spiked with 1.5 μg and 5 μg /mL DAM and COD, respectively. As only 0.1% of a DAM dose is excreted unchanged in urine (14) this ACOD artifact formation observed after using a very high DAM concentration might not be relevant when analyzing real urine samples. The COD levels, resulting from COD ingestion and ACOD metabolism, varied between 0 and 32,600 ng/mL, with mean peak concentrations

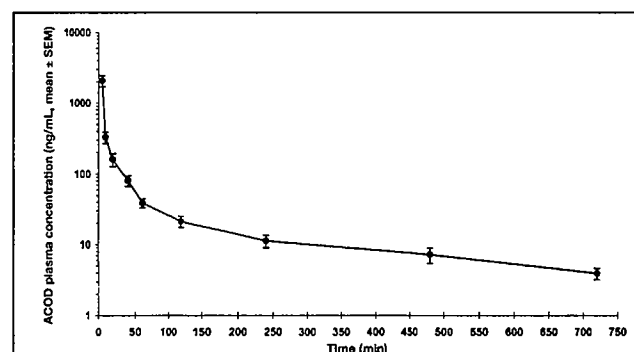


Figure 1. ACOD plasma profile after an i.v. bolus of 5 mg ACOD, opiate-naïve subjects (mean \pm SEM, $n = 10$).

Table II. Pharmacokinetics of ACOD in Opiate-Naïve Subjects ($n = 10$) after an i.v. Bolus of 5 mg ACOD

	Subject										Mean	SEM
	A	B	C	D	E	F	G	H	I	K		
Gender	f	m	m	f	m	m	f	m	f	f		
$t_{1/2}$ (min)	232	193	311	238	254	225	284	110	221	300	237	18
V_z (L)	44	27	185	86	58	102	92	28	86	105	81	15
CL_{tot} (mL/min)	132	97	411	252	159	314	224	177	268	244	228	29

of 8882 ± 3320 ng/mL in the 2-h urines (Table IV). In order to avoid false-positive ACOD results consecutively leading to unjustified assumption of street heroin consumption, we recommend quantitation of both ACOD and COD and calculation of the COD/ACOD ratio. Mean COD/ACOD ratios of 874 ± 285 (2-h urine), 4245 ± 1632 (4-h urine) and 2509 ± 2053 (8-h urine) resulted from the DAM-COD co-administration experiments, whereas the ratios from the pharmacokinetic (Table III) and the

field study varied from 0 to 3614 (178 ± 181) and from 0 to 47 (2 ± 2), respectively.

Feasibility studies with HAT program participants

During the summer of the year 2000, a total of 105 urine specimens were collected at HAT centers located in three different cities in Switzerland ("field study"). Basing on the data of the pharmacokinetic and the transacetylation study,

Table III. ACOD and COD Urine Levels and COD/ACOD Ratios in Opiate-Naïve Subjects ($n = 10$) after an i.v. Bolus of 5 mg ACOD

Subject	Time (h)						
	0	2	4	8	12	24	48
ACOD Concentration (ng/mL)							
A	0	471.9	0.8	0	0	0	0
B	0	86.8	11.6	0	0	0	0
C	0	169.1	6.8	0	0	0	0
D	0	4.9	0.2	0	0	0	0
E	0	22.2	0.5	0	0	0	0
F	0	69.9	0.5	0	0	0	0
G	0	13.8	0.1	0	0	0	0
H	0	19.7	6.9	0	0	0	0
I	0	65.6	0.9	0	0	0	0
K	0	63.5	0.6	0	0	0	0
Mean	0	98.7	2.9	0	0	0	0
SEM	0	44.2	1.3	0	0	0	0
COD Concentration (ng/mL)							
A	0	597.5	451.8	60.0	51.0	91.7	6.6
B	0	673.1	562.8	140.0	n.a.	29.2	2.3
C	0	3720	316.8	38.8	68.5	82.7	5.3
D	0	8351	348.8	60.6	54.8	82.7	15.2
E	0	714.0	333.0	52.3	53.2	74.4	4.9
F	0	579.4	387.8	58.0	43.6	82.4	10.7
G	0	655.9	361.4	58.3	46.2	75.2	5.1
H	0	566.9	306.9	49.0	51.6	69.7	4.2
I	0	585.5	440.4	75.8	47.7	70.3	5.9
K	0	722.1	479.7	68.3	61.6	101.0	5.7
Mean	0	1717	398.9	66.1	53.1	75.9	6.6
SEM	0	798.5	26.1	8.8	2.5	6.0	1.2
COD/ACOD-Ratio							
A	0	1	565	0	0	0	0
B	0	8	49	0	0	0	0
C	0	22	47	0	0	0	0
D	0	1704	1744	0	0	0	0
E	0	32	666	0	0	0	0
F	0	83	776	0	0	0	0
G	0	9	3614	0	0	0	0
H	0	29	45	0	0	0	0
I	0	9	489	0	0	0	0
K	0	11	800	0	0	0	0
Mean	0	191	480	0	0	0	0
SEM	0	168	343	0	0	0	0

Table IV. ACOD and COD Urine Levels and COD/ACOD Ratios after the Co-administration of 120 to 400 mg DAM i.v. and 50 mg COD p.o. to HAT Participants ($n = 10$)

Subject	Time (h)			
	0	2	4	8
ACOD Concentration (ng/mL)				
A	0	2.1	0.2	0
B	0	5.4	0.4	2.1
C	0	10.7	0.8	0.1
D	0	2.3	0	0
E	0	4.3	3.2	0
F	0	30.6	1.2	0
G	0	62.8	1.6	0
H	0	69.6	0.8	0
I	0	1.5	33.7	7.0
K	0	147.0	3.6	5.0
Mean	0	33.6	4.6	1.4
SEM	0	15.0	3.3	0.8
COD Concentration (ng/mL)				
A	0	2198	1039	552.1
B	0	6785	5804	7678
C	0	6018	1667	2106
D	0	1142	191.0	109.2
E	0	3806	2256	109.5
F	0	23,554	9225	4826
G	0	2189	911.0	334.4
H	0	32,600	8666	4359
I	0	4765	1799	1646
K	0	5760	2911	688.3
Mean	0	8882	3447	2241
SEM	0	3320	1036	810
COD/ACOD-Ratio				
A	0	1047	5195	0
B	0	1256	14,510	3656
C	0	562	2084	21,060
D	0	497	0	0
E	0	885	705	0
F	0	770	7688	0
G	0	35	569	0
H	0	468	10,833	0
I	0	3177	53	235
K	0	39	809	138
Mean	0	874	4245	2509
SEM	0	285	1632	2053

samples with ACOD levels > LOQ and COD/ACOD-ratios > 0 and < 50 were considered as positive in respect of the use of street heroin in the last 24 h. In consequence, 15 (14%) samples were positive, containing 0.3 to 103 ng/mL ACOD (22.1 ± 9.4 ng/mL) and 0.5 to 3309 ng/mL COD (553.3 ± 295.3 ng/mL), respectively (Table V). The COD/ACOD ratios ranged from 0.4 to 47 (15 ± 5). Only traces (< LOQ) of ACOD could be detected in 20 samples (19%) with traces to 160 ng/mL of COD. These urines were regarded as negative. It is noteworthy that none of the subjects reported a COD medication in the past 48 h, meaning that ACOD formation by transacetylation is not very likely. No ACOD-positive urines resulted from another study with 44 HAT participants (8). We assume that this discrepancy could be due to other collection conditions (time, site etc.), differences in the HAT programs (other DAM dosage schemes, better psychosocial and medical care), more strictly enforced heroin street market and/or the less sensitive analytical method used (LOQ 1 ng/mL) in the study of Staub et al. (8). It has to be mentioned that 30% of the ACOD-positive urines from our feasibility field study were in the concentration range \geq LOQ and < 1 ng/mL.

The concomitant use of DAM and cocaine [e.g., by injection of a mixture of both drugs ("speedball")] is still popular in Switzerland. Whereas 81% of HAT participants declared daily heroin consumption before entering the programs, 25% also reported daily cocaine use (1). Consequently, to check for a possible correlation between the simultaneous presence of ACOD and cocaine in urine, all samples were analyzed by a non-instrumental immunoassay (Frontline). Thirty percent of all urines tested positive for cocaine, and 67% of the ACOD-positive urines were also cocaine positive (Table V). To validate the

self-declaration as a suitable instrument for monitoring street heroin consumption, all participating subjects were asked to frankly report their heroin and cocaine consumption outside HAT centers in the last 24 to 72 h. Although the self-reporting of drug use by face-to-face interview (standardized questionnaire) was performed under confidential conditions and, also in case of ACOD-positive testing, without any consequences for the HAT participants, the concordance of positive results based on self-reporting and ACOD monitoring was unexpectedly rather low (53%). It has to be noted that under-reporting of drug use is a well-known phenomenon (15). No significant correlation was found between the day, time, and place of sample collection and the ACOD positives.

Recently, Bogusz et al. (16) proposed the use, in addition to ACOD, of the native opium alkaloids noscapine and papaverine for the differentiation of prescribed and non-prescription heroin. As these compounds are, at least in Switzerland, constituents of a few medicaments, interferences may not be excluded. On the other hand, the simultaneous presence of all three compounds in urine could provide a strong evidence for street heroin consumption. Therefore, 15 ACOD-positive urines from the "field study" were randomly selected and reanalyzed by GC-MS for the presence of noscapine and papaverine. Eight urines contained besides ACOD 0.1–183 ng/mL noscapine and 0.1–1.9 ng/mL papaverine, respectively. One specimen contained ACOD and noscapine, and six contained ACOD only. A peak concentration of 6 ng/mL noscapine was measured in the urine of a patient who ingested 30 mg noscapine hydrochloride as a cough medication. After about 30 h, the detectability was much longer than that of ACOD. It has to be noted that the described GC-MS method for the determination of ACOD must be slightly modified for the simultaneous detection of ACOD, noscapine, and papaverine.

Conclusions

A pharmacokinetic study on opiate-naïve subjects with a low i.v. dose of ACOD has revealed its rapid metabolism by deacetylation and elimination from the body. Only a small fraction ($0.4 \pm 0.1\%$) of the dose was recovered unchanged in urine, resulting in a rather narrow urine detection window. ACOD is also formed by in vivo transacetylation of simultaneously ingested COD and during GC-MS analysis when coinjecting high concentrations of DAM and COD in a urine matrix. Despite these limitations we think that ACOD may be used in HAT programs as a socio-medical quality control tool for the detection of recent street heroin consumption, provided that COD/ACOD-ratios are calculated to avoid false-positive results. The inclusion of other street heroin constituents (noscapine, papaverine) could increase the reliability of the ACOD monitoring, for example when used for forensic purposes, but more pharmacokinetic and field studies that include heroin users outside HAT programs, are necessary. As there was a certain correlation between the simultaneous presence of ACOD and cocaine in urine, cocaine-positive results can be considered as an additional hint for street heroin/cocaine ("speedballs") consump-

Table V. Street Heroin Consumption by HAT Participants ($n = 105$, feasibility study) Detected by ACOD Urine Marker and Self-Report

Sample	Concentration (ng/mL)		COD/ACOD Ratio	Cocaine	Self-Report*
	ACOD	COD			
1	31.9	760.1	24	pos	yes
2	0.5	0.6	1	neg	no
3	0.3	1.3	4	pos	no
4	0.7	5.3	8	neg	no
5	11.5	181.3	16	pos	yes
6	20.0	435.5	22	pos	yes
7	0.4	0.5	1	neg	no
8	49.4	2000	40	neg	yes
9	20.3	235.7	12	pos	yes
10	0.5	1.2	2	pos	yes
11	1.5	0.6	0.4	neg	no
12	10.7	502.8	47	pos	yes
13	66.5	861.0	13	pos	yes
14	103.3	3309	32	pos	no
15	13.6	5.3	0.4	pos	no
Mean	22.1	553.3	15		
SEM	9.4	295.3	5		

* Street heroin consumption in the last 72 h reported confidentially by the HAT participants.

tion. It seems, that even when performed confidentially, the self-reporting is not much suited as monitoring instrument for street heroin consumption.

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